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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,508	01/07/2003	Alejandro Abuin	P32426	9495

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SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,508	ABUIN ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: _____.

DETAILED ACTION

This Application, filed January 7, 2003 is a 371 of PCT/GB00/03747, filed September 29, 2000, and claims priority to foreign application 9923334.8, filed October 1, 1999, in the United Kingdom.

Claims 1-16 are pending.

Specification

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Page 14 of the specification, section 1.3 lists two primers. No SEQ ID NOs have been assigned to these sequences. A SEQ ID NO. must be assigned to each of these primers. Applicant must provide these sequences on disk and

paper format and a statement indicating that these the paper copy and disk are the same must be included.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence comprising SEQ ID NO. 1, wherein SEQ ID NO. 1 encodes human uncoupling protein 3 (UCP3), operably linked to a human skeletal muscle specific alpha-actin promoter, wherein the transgenic mouse exhibits weight loss, does not reasonably provide enablement for any transgenic rodent comprising a human UCP3 polypeptide under the control of any regulatory sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8

USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention is drawn to a transgenic rodent comprising a transgene construct comprising a nucleic acid sequence encoding human UCP3 operably linked to a promoter. The claimed invention is also drawn to a method of making and using the transgenic rodent comprising a transgene comprising UCP3. The specification teaches a transgene construct comprising a nucleic acid sequence (SEQ ID NO. 1) encoding human UCP3 was operably linked to a human skeletal muscle specific alpha-actin promoter (specification, page 14, sections 1.1 and 1.2). The specification also teaches that the transgene was excised from the vector and the gel-purified 3.9 kb fragment was injected into male pronuclei of fertilized eggs (specification, page 14, section 1.5). The specification teaches that 10-12 mice comprising the transgene exhibited a

reduced body weight, despite showing an increased 24h-food intake (specification, page 15, 2nd parag.). The specification teaches that glucose disposal was greater in 10-12 human UCP3 transgenic mice than in wild type mice (specicificaton, page 15, 3rd parag.). While the specification provides these teaching the specification does not provide guidance to the artisan to practice the claimed invention for its full breadth.

The claimed invention broadly encompasses a transgenic rodent comprising a transgene construct stably inserted in its genome a nucleic acid sequence encoding human UCP operably linked to any promoter. While the claimed invention broadly encompasses any transgenic rodent, the art at the time of filing teaches that an artisan cannot predictably use any transgene construct to make a transgenic animal in different species of rodent. For example, Hammer et al. (1990, Cell, 6: 1099-1112) created both transgenic mice and rats expressing the human HLA-b27 gene and beta-2 microglobulin. Although both transgenic animals bearing the HLA-b27 gene expressed the gene, transgenic mice did not show any HLA-b27 associated disease, whereas the transgenic rats demonstrated most of the HLA-b27 related diseases (Hammer, et al., page 1099, col. 2, lines 20-28). This shows that the integration of a transgene into an alternative species may result in widely different phenotype responses even in animals of the same species, rodents. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. Further, some transgene products may require factors to function, which may not be present in other species of animals. With regards to

the instant invention, the specification teaches a transgene construct comprising a nucleic acid sequence (SEQ ID NO. 1) encoding human UCP3 was operably linked to a human skeletal muscle specific alpha-actin promoter (specification, page 14, sections 1.1 and 1.2) was used to generate the transgenic mice described in Example 2. The specification teaches that the transgenic mice exhibited weight loss. While the specification teaches these embodiments of transgenic mice, the specification does not teach that other rodents comprising the transgene have a similar phenotype. Given the teachings of Hammer et al. above, an artisan cannot predict whether the transgene construct necessarily works in other rodents such as rats, guinea pigs, and hamsters. Further, an artisan cannot predict that the human UCP3 has a similar activity in rats, guinea pigs, and hamsters. For this reason, an artisan is not enabled for the full scope of making any transgenic rodent.

The claimed invention broadly encompasses the use of any "regulatory sequence facilitating expression of said polypeptide," or promoter. While the specification teaches a transgenic mouse comprising a nucleic acid sequence encoding human UCP3 operably linked human skeletal muscle alpha-actin promoter, the specification does not teach other rodents comprising other tissue specific promoters, other muscle specific promoters, and ubiquitous promoters. Again, referring to Hammer et al., discussed above, an artisan cannot predict that one promoter will necessarily work in another species of animal. An artisan cannot predict that any tissue specific promoter will necessarily have the same activity in a transgenic animal. This is illustrated by Cowan et al. (2003,

Xenotransplantation, 10: 223-231). Cowan et al. teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs. With regards to the instant invention, while the specification teaches that the human skeletal muscle alpha-actin promoter has activity in transgenic mice, no guidance has been provided that the same promoter has activity in other rodents such as rats, hamsters, and guinea pigs. Regarding the use of ubiquitous promoter such as the CMV promoter, the art teaches that these promoters express constitutively in all types of tissue. The specification teaches that UCP3 mRNA is expressed predominantly in skeletal muscle (specification, page 4, lines 14-18). The art teaches that UCP3 is also expressed at much lower levels in the heart and kidney and occasionally in white adipose tissue (Giacobino et al., U.S. Patent 6,620,594, patented September 16, 2003, col., 8, lines 56-59). While the claims encompass a transgenic rodent comprising a transgene construct comprising a nucleic acid sequence encoding human UCP3 operably linked to CMV, the specification does not teach an artisan if there is expression of human UCP3 in other tissues and if any of these tissues

exhibit any phenotype. Additionally, nothing in the specification teaches that introduction of a construct comprising a nucleic acid sequence encoding human UCP3 operably linked to a CMV promoter drives enough expression of UCP3 such that a phenotype can be detected. For this reason, the specification enables an artisan to practice the claimed invention for only a human alpha-actin promoter.

With regards to the broad scope of any rodent, the art at the time of filing teaches that making any transgenic animal was unpredictable. One reason for this unpredictability stems from the randomness in which the transgene integrates into the host's genome. Cameron (1997, Molecular Biotechnology, 7: 253-265) teaches, "a feature common to many transgenic experiments is the unpredictability transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene (Cameron, page 256, section 4 on transgene regulation and expression)." Thus, an artisan cannot predict where a transgene will integrate in the host genome, how many copies of a transgene will integrate into the host genome, what the transgene expression pattern is, of the resulting transgenic animal (with regards to how much transcript is produced by the cell and with regards to in which tissues express transgene, as enhancers from the host's genome may also influence transgene expression), and what the subsequent phenotype(s) is of the transgenic animal. As summarized by Mench

(1999, Transgenic Animals in Agriculture, eds. Murray et al., CAB International: Oxon, pages 251-268), "because there can be so much variation in the sites of gene insertion, the numbers of gene copies transferred, and gene expression, every transgenic animal produced using microinjection is (theoretically, at least) unique in terms of its phenotype (Mench, page 259, bottom)." With regards to the instant invention, an artisan cannot predict what kind of phenotypes would result from the introduction of any transgene construct to any rodent. While the specification teaches that transgenic mice were made, nothing in the specification teaches that the same construct would necessarily produce other transgenic rodents exhibiting a phenotype similar to the mouse. To determine the possibility that the construct could be used in other rodents would need to be empirically determined. For this reason, an artisan is not enabled for the full scope of any rodent.

Claims 1-8 encompass a transgenic rodent that has no phenotype. Nothing in the specification teaches an artisan how to use a transgenic rodent comprising a transgene construct comprising a nucleic acid sequence encoding human UCP3 operably linked to any promoter, wherein the transgenic animal has no phenotype. As such, because an artisan does not know how to use a transgenic rodent that exhibits no phenotype, an artisan does not know how to use the claimed animal in a method for determining the phenotypic effect of the compound (claim 15).

The claimed invention encompasses a transgenic rodent wherein the transgenic rodent exhibits increased wound healing (claim 10). While the

specification teaches that UCP3 has been correlated with wound healing (specification, page 4, 2nd parag.), the specification does not teach an artisan that the transgenic mice described in the instant specification has a wound healing phenotype. Nothing in the specification teaches that the transgene construct used in the transgenic mice indicated that human UCP3 expressed in these mice had a role in wound healing. While the specification teaches that expression of human UCP3 in mouse muscle resulted in weight loss and an increase in glucose disposal in mice, nothing in the specification indicates that human UCP3 had other biological activities in these transgenic mice. Again, referring to Hammer et al. above, an artisan cannot predict that all species of animals express the same set of cellular factors. Subsequently, while the function of human UCP3 in muscle regarding weight loss (specification, Figure 1) and an increase in glucose disposal (specification, Figure 2) appears to be conserved between human and mouse, an artisan cannot assume that the function of human UCP3 in wound healing is necessarily the same between mouse and human. Additionally, while the specification teaches that what level of expression of human UCP3 that was expressed in muscle resulted in weight loss, nothing in the specification indicated that the human UCP3 was expressed at high enough levels in muscle that a wound healing phenotype could be seen. While this discussion was to indicate that the specification does not provide guidance for an artisan to use the claimed rodent as a model for wound healing, the discussion also applies to the other phenotypes claimed in claim 15: obesity, diabetes, hyperlipidaemia, body weight disorders, wound healing, cachexia, inflammation,

tissue repair, and atherosclerosis. The specification teaches that the transgenic mice described in the specification exhibits weight loss and an increase in glucose disposal, the specification does not indicate whether the transgenic mice exhibited any other phenotypes. Further, nothing in the specification teaches what relationship the weight loss and increased glucose disposal exhibited in these mice has to do with any disease such as obesity, diabetes, hyperlipidaemia, body weight disorder, wound healing, cachexia, inflammation, tissue repair, and atherosclerosis. Nothing in the specification indicated that the human UCP3 protein expressed in the transgenic mice had biological activity related to the other disorders listed in claim 15. As such, if human UCP3 does not have any biological activity related to these phenotypes, an artisan would not know how to use the animal in a screen for compounds that alter the phenotypes.

Claims 2i and j use the term "Identity Index." The specification teaches what is meant by "identity" (specification, pages 11-13), but the specification does not teach what is meant by "Identity Index." A search on Google did not turn up any definitions. Subsequently, an artisan cannot practice the claimed invention using the parameter "Identity Index" without any guidance.

Therefore, for the reasons described above, the scope of the claimed invention is not commensurate with the teachings of the specification.

Claims 1-3 and 6-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification provides adequate written description for the polynucleotide encoding human UCP3 polypeptide as designated by SEQ ID NO. 1, and a polypeptide encoding human UCP3 as SEQ ID NO. 2, the specification fails to adequately describe other nucleic acid sequences which encode human

UCP3 and provide activity to human UCP3, such that a phenotype can be seen in the transgenic animal. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, while the claims (see claim 2) encompass a polynucleotide sequence that:

(claim 2a, c) "have" or "comprise" a polynucleotide sequence that has at least 95-99% identity to the polynucleotide of SEQ ID NO.1,

(claim 2b) "comprise" the polynucleotide of SEQ ID NO. 1,

(claim 2e/g) "have" or "comprise" a polynucleotide sequence encoding a polypeptide sequence having at least 95-99% identity to the polypeptide sequence of SEQ ID NO. 2,

(claim 2f) "comprise" a polynucleotide sequence encoding the polypeptide of SEQ ID NO. 2,

(claim 2i) "have" or "comprise" a polynucleotide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to the polynucleotide sequence of SEQ ID NO. 1

(claim 2j) "have" or "comprise" a polynucleotide sequence encoding a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to the polypeptide sequence of SEQ ID NO. 2,

the specification does not teach what 1-5% of the sequence may be changed, yet still confer activity to human UCP3. Here, activity, as taught by the specification, is the weight loss seen in the specification, Figure 1, and the increased glucose disposal seen in specification, Figure 2. With regards to "Identity Index," the Examiner has interpreted the term to be the same as "percent identity" as written in claims 2a, c, e, and g. As such, like "percent identity," nothing in specification teach an artisan what about the "Identity Index" can be altered such that an artisan could obtain a human UCP3 sequence with the similar biological activity of UCP3. With regards to the words, "comprising" and "having," the word encompasses partial sequences of SEQ ID NO. 1. While this may be intended to be encompassed by the claimed invention, nothing in the specification teaches an artisan how to obtain a partial sequence of SEQ ID NO. 1, or a partial sequence of a nucleotide sequence encoding the polypeptide of SEQ ID NO. 2, such that when expressed, produces the phenotype taught by the Applicant in the Examples. The skilled artisan cannot envision all the possible variant nucleic acid sequences which would hybridize and encode a human UCP3 with activity that results in weight loss and an increase in glucose disposal, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference

to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a nucleic acid sequence of SEQ ID NO. 1 and a polynucleotide encoding the polypeptide of SEQ ID NO. 2 (claim 2, c and h) meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11a recites the limitation "the gene of interest" in claim 1. There is insufficient antecedent basis for this limitation in the claim. There is no "gene of interest" in claim 1.

Claim 11c recites the limitation "the transgene" in claim 1. There is insufficient antecedent basis for this limitation in the claim. There is no "transgene" in claim 1. Alternatively, "the transgene" might refer back to the "transgene construct" in claim 11a. If this is the case, this is unclear because a

"transgene" is comprised of one gene, whereas a "transgene construct" is comprised of the transgene and a promoter operably linked to the transgene.

Claim 11d recites the limitation "the injected eggs." There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites the limitation "mouse ES cells" in claim 11. There is insufficient antecedent basis for this limitation in the claim. There are no mouse ES cells in claim 11. In addition to this, claim 12 involves method steps which are entirely different from those is claim 11. In addition to using different cells to introduce the transgene (ES cells versus fertilized egg), claim 12 uses different steps for introducing the transgene from claim 11 (pronuclear injection).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

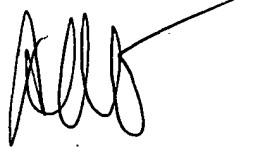
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER



Application No.:
10/089,508

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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